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Evidence-Based Treatment of Premenstrual Dysphoric Disorder: A Concise Review

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Premenstrual dysphoric disorder (PMDD) is a collection of physical, cognitive, and affective symptoms causing clinically significant distress or interference that occur in the 7 days prior to the onset of menses, after which they become minimal or absent.¹ The diagnosis is established by symptom documentation using a validated, reliable tool such as the Daily Record of Severity of Problems (DRSP) for at least 2 menstrual cycles to confirm the timing of relevant symptoms.^{2,3} According to the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, there is a 1.8%–5.8% 12-month prevalence of PMDD among menstruating women¹; however, the prevalence of premenstrual symptoms causing clinically significant interference or distress but not meeting full criteria for a diagnosis of PMDD may be as high as 13%–18%.⁴ Women with PMDD suffer functional impairments comparable to other depressive disorders, and yet PMDD and its impact remain underrecognized.⁴

Emerging evidence supports the theory that the sharp rise in ovarian steroid hormones and their metabolites produces the negative mood symptoms of PMDD in vulnerable women.⁵ In particular, the action of metabolites of progesterone, particularly allopregnanolone, on GABA-A receptors has been proposed as a mechanism in the pathophysiology of PMDD,⁶ although some evidence implicates estradiol.⁵ Further research is required to illuminate the definitive pathophysiology, but treatments targeting various proposed mechanisms have arisen. This review concisely summarizes the evidence for current PMDD treatment options as evidenced from randomized, placebo-controlled trials. Medications used in clinical practice, such as danazol for suppression of ovulation or alprazolam for symptomatic treatment of premenstrual anxiety, that have not been studied in randomized, placebo-controlled trials in PMDD were excluded, as were complementary and alternative medicines with similarly limited evidence.

Selective Serotonin Reuptake Inhibitors

Large trials have established that luteal phase dosing, ie, administering medication only in the 14 days preceding menses, of selective serotonin reuptake inhibitors (SSRIs) is an effective

treatment for PMDD when compared to placebo.^{7–11} Agents and doses shown to be effective with luteal dosing are sertraline 50–100 mg, fluoxetine 20 mg, paroxetine 10–20 mg, and escitalopram 10–20 mg. Studies conducted to compare continuous dosing versus luteal phase dosing of SSRIs in parallel or crossover designs have found that both strategies are efficacious.¹⁰ Meta-analyses comparing luteal phase dosing versus continuous daily dosing have been mixed, with one demonstrating a greater benefit for continuous dosing¹² and another finding no significant difference in efficacy between the two strategies.¹³ Symptom-onset dosing, ie, administering medication at the first onset of symptoms in a given cycle, of SSRIs has shown some efficacy,¹⁴ but a recent large-scale study demonstrated only modest benefit over placebo, with symptom-onset dosing groups failing to separate from placebo on the primary outcome measure but showing improvement in total DRSP score as well as the DRSP anger/irritability subscale.¹⁵ A single dose of fluoxetine 90 mg given 14 days prior to menses and 90 mg again 7 days prior to menses has also been shown to be effective for PMDD in one trial.¹⁶ In addition to the well-demonstrated efficacy of SSRIs for PMDD for a variety of dosing strategies, intermittent dosing of SSRIs is shown to be well-tolerated and not associated with significant discontinuation symptoms compared to placebo.⁷ Clinicians prescribing SSRIs for PMDD should consider the long-term tolerability of the chosen medication as well as reproductive goals of the patient.

Oral Contraceptives

Although they are commonly used, to date, no randomized, placebo-controlled trials of any formulation of oral contraceptives (OCPs) dosed in the standard method of 21 days of active pills followed by 7 days of placebo pills have demonstrated efficacy over placebo for PMDD. The most robust evidence supporting the use of OCPs to treat premenstrual symptoms comes from trials of combination drospirenone and ethinyl estradiol (EE) dosed for 24 active days and 4 inactive days, which produced significant reduction in premenstrual symptoms compared to placebo.^{17–19} Another trial of combination drospirenone/EE dosed as 21 active days and 7 inactive days in a sample of women with PMDD showed no efficacy compared to placebo.²⁰

Following the hypothesis that fluctuations rather than steady-state hormone levels are responsible for premenstrual mood symptoms,⁵ researchers hypothesized that continuous dosing of OCPs without a regular hormone-free period might be more efficacious than traditional dosing designed to produce withdrawal menses. One trial of continuous combination levonorgestrel and EE for women with PMDD demonstrated that active treatment was significantly more beneficial than placebo, but continuous dosing was not compared against intermittent dosing in that trial.²¹ However, a recent small trial of combination drospirenone/EE failed to demonstrate superiority of the continuous dosing regimen over the traditional hormone-free interval dosing regimen, and neither active treatment group separated from placebo.²²

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To cite: Carlini SV, Deligiannidis KM. Evidence-based treatment of premenstrual dysphoric disorder: a concise review. *J Clin Psychiatry*. 2020;81(2):19ac13071.

To share: <https://doi.org/10.4088/JCP.19ac13071>

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Leuprolide

Leuprolide, a gonadotropin releasing hormone (GnRH) agonist that induces ovarian suppression, has been shown to reduce premenstrual symptoms when dosed monthly as a 3.75 mg depot compared to placebo.²³ Although a meta-analysis concluded that add-back hormone therapy to reduce the side effects of ovarian suppression does not sacrifice efficacy,²⁴ leuprolide has a significant side effect burden and should be reserved for severe cases that are refractory to SSRIs and OCPs.

Novel Pharmacotherapies

The emergence of evidence implicating allopregnanolone in the etiology of PMDD^{5,6} has led to novel drug development. A phase 2 study in a sample of women with PMDD of sepranolone, an allopregnanolone antagonist, conducted over the length of 1 menstrual cycle demonstrated that patients receiving the active compound had significant reduction in symptoms compared to placebo as measured by the total score of the DRSP.²⁵ Sepranolone was dosed as a 10-mg or 16-mg subcutaneous injection standardized to 0.4 mL every other day during the luteal phase for a total of 5 injections, with the first injection occurring at ovulation.²⁵ In addition to the primary outcome of reduction in DRSP total score, secondary outcomes of reduction in DRSP negative mood score (a subscale composed of the sum of depression, anxiety, lability, and anger/irritability items) and reduction in a functional impairment score were also compared between groups.²⁵ Marginally significant reductions in functional impairment ($P = .091$) and DRSP negative mood score ($P = .051$) were found in the active treatment group compared to placebo.²⁵ Additionally, there was no significant difference in frequency of adverse events between groups, with the most common adverse event being injection site reaction, leading the study authors to conclude that this suggests a favorable safety profile compared to the established treatment protocols with SSRIs and OCPs.

CONCLUSION

PMDD is a cyclical mood disorder affecting a subset of menstruating women with a disease burden comparable to that of other depressive disorders. A significant body of evidence supports the use of SSRIs dosed either continuously or during the luteal phase as an effective first-line treatment for PMDD. OCPs containing drospirenone/EE or levonorgestrel/EE are an accepted second-line therapy despite limited evidence. For refractory cases, ovarian suppression may be considered. Novel investigative pharmacotherapies targeting the proposed neuroendocrinologic underpinnings of PMDD are emerging and stand to challenge this established treatment paradigm. Further research is needed to both continue to elucidate the pathophysiology of this disorder and establish its most efficacious treatments.

Published online: February 4, 2020.

Potential conflicts of interest: The authors report no potential conflict of interest related to the current topic. Dr Deligiannidis has received research grant support from Sage Therapeutics and Vorso Corporation, served as a consultant to Sage Therapeutics, and receives royalties from a National Institutes of Health Employee Invention.

Funding/support: None.

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